Learning Objectives

1. To understand the controversy over the existence of Amiodarone associated optic neuropathy (AAON).
2. To appreciate what are the legitimate clinical characteristics of AAON.
3. To be able to distinguish AAON from AION.

CME Questions

1. The duration of optic disc edema in AAON is:
   a) 6 weeks
   b) 8 weeks
   c) 12 weeks or more

2. Which of the following is NOT compatible with the diagnosis of AAON:
   a) bilateral simultaneous optic disc edema
   b) peripheral visual field loss
   c) sudden onset of visual loss
   d) possible visual recovery after drug is discontinued

3. The appropriate response to a patient with disc edema who is taking amiodarone:
   a) do nothing
   b) stop amiodarone
   c) contact cardiologist to discuss the issue
   d) follow the patient with sequential examinations and visual fields

Keywords: Amiodarone, anterior ischemic optic neuropathy

Amiodarone is an alpha and beta antagonist used in the treatment of cardiac arrhythmias, particularly atrial fibrillation, and has gained great popularity as an anti-arrhythmic drug in the United States. Several side effects have been noted with the use of amiodarone including thyroid dysfunction, peripheral neuropathies and pulmonary toxicity. In a series of articles, optic nerve dysfunction has also been identified as a side effect of amiodarone. There are, however, questions that remain regarding the existence of a true amiodarone-associated optic neuropathy (AAON). If it does exist, its clinical characteristics, frequency and natural history are still the subject of medical and legal debate.

IDENTIFICATION

Some reports on AAON have identified this entity as any optic neuropathy that occurs in a patient taking amiodarone. One problem with this definition is that every optic neuropathy that occurs in a patients taking amiodarone cannot automatically be implicated as being associated with the drug. Taking amiodarone does not protect the patient from other forms of optic neuropathy. Therefore, it behooves us to identify, if possible, amiodarone associated optic neuropathy and to define its clinical parameters.

FREQUENCY

There is really no true figure as to the frequency/incidence of this disorder. In one report, there were 447 patients who were examined and 9 had visual loss and/or disc edema. One patient had biopsy-proven giant cell arteritis and was eliminated. In the same article, additional patients included were from another institution but the number of patients surveyed from which these five patients were extracted was not identified in the paper. The authors therefore suggest an incidence of AAON of 1.79%.

The real conundrum in the optic neuropathy associated with amiodarone usage is whether this is an optic neuropathy caused by the amiodarone or whether it is a run-of-the-mill non-arteritic ischemic optic neuropathy (NAION) in this age group. The incidence figure often quoted for NAION is 0.3% in patients over 50 years of age. However, these data are from Olmsted County, Minnesota and do not take into account, aside from age, the medical history of the patient. It is therefore entirely possible and, in fact, likely that a group of patients who require treatment with amio-
Darone have a vascular substrate that would predispose them to NAION at a higher rate than in a general population. Studies have not been performed to indicate what the incidence of NAION is in a group of patients similar to those treated with amiodarone.

Since the total number of patients who develop proposed AAON is quite small and because it is not possible to do a placebo controlled study in patients who require amiodarone, the existence or non-existence of this entity must be left to clinical determinations. In other words, Do patients taking amiodarone develop an optic neuropathy that is clinically distinct from NAION? If the clinical profile is exactly the same as NAION, it would be unreasonable to propose that amiodarone causes a separate optic neuropathy. If, however, patients develop a form of optic neuropathy that is distinct or distinctly unusual for that which we diagnose as NAION, the likelihood exists that this is a separate optic neuropathy. However absent, a controlled study the preponderance of evidence for or against the existence of amiodarone-associated optic neuropathy is circumstantial.

CLINICAL CHARACTERISTICS
The clinical characteristics of NAION are well known. They include:

1. The sudden onset of visual loss, usually in the morning upon awakening
2. The presence of a swollen optic disc that may be sectoral in nature
3. Signs of an optic neuropathy including decreased visual function, visual field defects and a relative afferent pupillary defect
4. The visual deficit may progress over a period of two to three weeks but then stabilizes
5. The optic disc structure in the contralateral uninvolved eye is characteristic (congenitally anomalous disc)\(^3\)
6. The disc edema subsides almost invariably within eight weeks
7. Patients are prone to develop a second episode of NAION in the contralateral eye months or years following the initial event
8. There is almost always residual visual loss even though it is said that over 40% of people experience some improvement in visual function.\(^7\)

Therefore there are several possibilities with regard to the optic neuropathy seen in patients taking amiodarone:

1. Amiodarone does not produce an optic neuropathy and that which is seen in patients taking amiodarone is coincidental NAION
2. Patients on amiodarone have a higher incidence of NAION that is somehow related to the ingestion of drug
3. There is a separate identifiable form of optic neuropathy that is a toxic optic neuropathy associated with amiodarone ingestion

There is no evidence that the optic neuropathy purported to be associated with amiodarone is an ischemic event. In fact, it is more likely a toxic optic neuropathy. In order to diagnose a toxic optic neuropathy, several criteria should be found:\(^4\)

(1) Temporal relationship to the optic neuropathy and ingestion of the drug

The side effect of any amiodarone-associated optic neuropathy is said not to occur before one month of drug therapy. This may not be true. There is no guarantee that this conclusion drawn from the Mayo Clinic Study\(^1\) was AAON. There are no known specific time relationship between drug ingestion and any optic neuropathy.

(2) Absence of an alternative cause

This is a critical issue since many of the cases in the literature would be diagnosed as NAION if the patient was not taking amiodarone. Therefore, it behooves the diagnostician to not make the diagnosis of AAON an entity that would otherwise be classic NAION.

(3) Withdrawal leads to improvement and re-challenging may lead to worsening of vision

There is evidence of improvement in some patients when amiodarone was discontinued. I am not aware of a specific re-challenge.

(4) There has to be a reason to suspect a cause/effect relationship

Histopathologic studies show inclusion bodies in various tissues of the eye that support the theory of
drug-induced lipoidosis. One optic nerve specimen (in a patient who did not have an optic neuropathy) also showed cytoplasmic lamellar inclusions in the large axons. It is speculated these inclusions can cause primary lipoidosis and therefore amiodarone optic neuropathy. The duration of amiodarone is up to 100 days and would therefore explain the insidious onset and prolonged disc swelling in AAON.

5) Previous human or experimental evidence that would support the existence of the toxic optic neuropathy

Several studies have described patients taking amiodarone who develop an optic neuropathy that is uncharacteristic of NAION. These clinical features would not be considered NAION and therefore are more likely to be something else, i.e. amiodarone-associated optic neuropathy.

6) There may be a dose responsive cause/effect relationship

This information is not known.

By these criteria, the clinical scenario that would necessarily indicate a toxic optic neuropathy due to amiodarone are:

1. An optic neuropathy developing months after institution of amiodarone therapy
2. Clinical characteristics sufficiently different from other optic neuropathies especially NAION
3. A clinical course uncharacteristic of another optic neuropathy.

The clinical characteristics as described by Macaluso et al. and Nagra and associates are sufficiently different from NAION to be considered a different entity, amiodarone associated optic neuropathy.

The clinical characteristics of the optic neuropathy that are likely associated with amiodarone toxicity are seen in the Table:

<table>
<thead>
<tr>
<th></th>
<th>Amiodarone</th>
<th>NAION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of symptoms</td>
<td>Insidious</td>
<td>Acute</td>
</tr>
<tr>
<td>Latenality</td>
<td>Bilateral, simultaneous</td>
<td>Unilateral</td>
</tr>
<tr>
<td>Duration of disc swelling</td>
<td>Months 6-8 weeks</td>
<td></td>
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</tbody>
</table>

These features are distinctly uncharacteristic of NAION and when present may reasonably be considered to be amiodarone associated optic neuropathy.

References


CME Answers

1. C
2. C
3. C